Two Forms of 2-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-1,3-*O*-benzylideneglycerol

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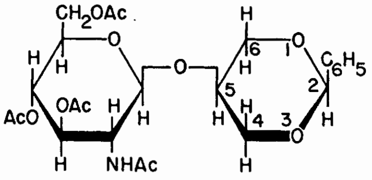
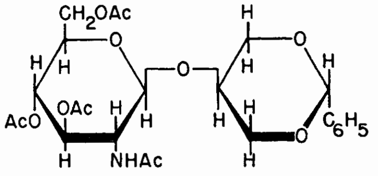
IN order to establish the configuration of the (1→4)-glycosidic linkage of 2-amino-2-deoxy-D-glucopyranose to D-glucuronic acid in heparin[1] the synthesis of 2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-1,3-*O*-benzylideneglycerol was undertaken. Treatment of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[2] with *cis*-1,3-*O*-benzylideneglycerol[3,4] in the presence of mercury(II) cyanide in anhydrous benzene at room temperature for 2·5 days and crystallization of the product from ethanol–petroleum (30—60°) gave a crystalline material, in 20% yield, whose elemental analysis was consistent with the molecular formula for 2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-1,3-*O*-benzylideneglycerol, namely, $C_{24}H_{31}NO_{11}$. The crystalline material had m.p. 197—203°, $[\alpha]_D^{21}$ −10·0° (*c*., 1·97 in chloroform). Surprisingly, thin-layer chromatography on silica gel G with ethyl acetate development revealed the presence of two components. Separation by preparative thin-layer chromatography afforded approximately equal amounts of two crystalline substances (I) and (II). Substance (I) had m.p. 191°, $[\alpha]_D^{33}$ −8° (*c*., 2·06 in chloroform), and R_f 0·43 (thin-layer chromatography as above); substance (II) had m.p. 211—212°, $[\alpha]_D^{33}$ −9° (*c*, 2·12 in chloroform), and R_f 0·60. In both cases elemental analysis indicated the formula $C_{24}H_{31}NO_{11}$. The infrared spectra (potassium bromide) of substances (I) and (II) were similar but did show differences in the "finger-print" region.

Significantly, partial hydrolysis of substances (I) and (II) with 3% hydrochloric acid in aqueous ethanol (70%) followed by treatment of the product with acetic anhydride in pyridine gave in each case (83% yield) crystalline 2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-1,3-di-*O*-acetylglycerol[5] which had m.p. 150—152° and $[\alpha]_D^{33}$ −7° (*c*, 1·65 in chloroform). This result implies that both substances (I) and (II) possess the *β*-D-anomeric configuration. It is believed, therefore, that the substances represent a pair of stereoisomers as shown below:



(I)



(II)

Thus, for example Baggett and his co-workers[4] have shown that the *cis*- and *trans*-1,3-*O*-benzylideneglycerols were converted by treatment with aluminium isopropoxide to a mixture of both forms

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[2] D. Horton and M. L. Wolfrom, *J. Org. Chem.*, 1962, **27**, 1794; D. Horton, Organic Syntheses, in the press.

[3] H. S. Hill, M. S. Whelen, and H. Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2240.

[4] N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey, and D. H. Whiffen, *J. Chem. Soc.*, 1960, 2574.

[5] H. Tomomatsu, Ph.D. Thesis, The Ohio State University, 1965.

in which the *cis*-isomer predominated. In contrast equilibration with acid of the *cis*- and *trans*-2-*O*-benzyl ethers favoured the *trans*-isomer. Such difference in behaviour can be attributed[6] to the possibility for intramolecular hydrogen bonding in *cis*-1,3-*O*-benzylideneglycerol, which is not present in the *cis*-2-*O*-benzyl ether. Recently, Bishop and his co-workers[7] reported that thermal rearrangement of *O*-benzylideneglycerols can occur during gas–liquid chromatography. Thus, whereas *trans*-1,3-*O*-benzylideneglycerol showed four peaks on gas–liquid chromatography corresponding to the *cis*- and *trans*-isomers of 1,2- and 1,3-*O*-benzylideneglycerol, the stable *cis*-1,3-*O*-benzylideneglycerol could be chromatographed unchanged.

Heating a solution of compound (I) in benzene–chloroform (9 : 1, v/v) for 7 hours at reflux temperature resulted in the formation of (I) and (II). Compound (II) was unaffected, however, even when heated at reflux temperature in toluene–chloroform (9 : 1, v/v). It seems most probable, therefore, that compounds (I) and (II) are, respectively, *cis*- and *trans*-2-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-1,3-*O*-benzylideneglycerol where the *cis* and *trans* refer to the hydrogens on carbons 2 and 5 of the 1,3-dioxan ring.

The nuclear magnetic resonance spectra (measured on a Varian A-60 spectrometer using approximately 10% solutions in deuterochloroform with tetramethylsilane as an internal reference) showed the following signals (τ scale):

	NH	Ph·CH[8]	OAc (integral, protons)	NAc[9]
(I)	3·35	4·48	7·94(3), 7·98(6)	8·19
(II)	3·69	4·61	7·94(3), 7·98(6)	8·05

A significant difference is the displacement (0·13 p.p.m.) of the benzylidene-methine proton signal to high field in isomer (II) which has been assigned the *trans*-configuration. Baggett and his co-workers[8] have determined the nuclear magnetic resonance spectra of the *cis*- and *trans*-forms of several derivatives of 1,3-*O*-benzylideneglycerol. It is interesting to note that in all the pairs of compounds the τ-value of the benzylidene-methine proton for the *trans*-isomer was higher by an average of 0·1 p.p.m.

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[7] C. T. Bishop, F. P. Cooper, and R. K. Murray, *Canad. J. Chem.*, 1963, **41**, 2245.

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[9] H. Agahigian, G. D. Vickers, M. H. von Saltza, J. Reid, A. I. Cohen, and H. Gauthier, *J. Org. Chem.*, 1965, **30**, 1085; D. Horton, private communication.